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A proposed cybernetic system for sodium and potassium homeostasis: Coordination of aldosterone and intrarenal physical factors

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Aldosterone, the most potent naturally occurring mineralocorticoid, plays a major role in regulation of the amounts of both sodium and potassium in the body. The hormone acts on the kidney tubules to increase both sodium reabsorption and the secretion of potassium ions. Because of these two simultaneous actions, there would appear to be a conflict of interest in constructing a homeostatic regulatory system for the simultaneous maintenance of the balance of the two cations, sodium and potassium, by this one hormone. Because of the two concurrent actions of aldosterone, one might expect that changes in its activity would inevitably accomplish defense in the balance of one ion at the expense of the other. One might expect, for example, that increases in aldosterone secretion in response to sodium depletion would, while defending sodium balance, also produce potassium loss or, conversely, that after potassium ingestion the induced increase in aldosterone secretion would, in the course of promoting kaliuresis, cause unwanted sodium retention. Obviously, neither happens. In fact sodium balance remains stable in the face of wide changes in potassium intake and vice versa.

This analysis is concerned then with the question of how the kidney adjusts to variations in both sodium and potassium intake to compensate for the two concurrent actions of aldosterone and to enable the appropriate excretion of both cations. In particular, the presentation considers how changes in sodium and potassium intake affect intrarenal physical factors and how, in turn, these intrarenal changes are coordinated with changes in aldosterone secretion to compose a balanced control system which works to stabilize the balance of one cation while reacting to wide fluctuations in intake of the other. First, the hormonal responses to changes in sodium and potassium intake will be characterized. Then, an analysis of the simultaneous and complementary changes in intrarenal physical factors will be presented.

Responses of the renal-adrenal hormonal axis to changes in sodium and potassium balance

Effect of variations in sodium intake on renin and aldosterone. The well-known relationship of both plasma renin activity and urine aldosterone excretion to variations in sodium intake is illustrated in Fig. 1 [1–4]. These data were derived from a study of 53 normal subjects, most of whom were maintained on a constant dietary regimen. The 24-hr urinary sodium excretion, plotted on the abscissa, is taken to be an index of the state of sodium balance. Measurements were usually made after the subjects had been on a constant diet for five days. In some subjects, however, daily analyses were made, beginning on the first day of the constant regimen and continuing for up to 11 days.

The plots indicate how plasma renin activity and urine aldosterone excretion move dynamically in relation to the rate of urinary sodium excretion. Both hormones increase with sodium deprivation. Conversely, both fall to a minimum concentration when dietary salt is present in excess. Since urine aldosterone and plasma renin activity exhibit an entirely parallel relationship to changes in sodium balance, this provides strong circumstantial evidence that the aldosterone secretory response to changes in sodium balance is mediated largely via changes in renin activity (i.e., via angiotensin II generation). Moreover, the hyperbolic

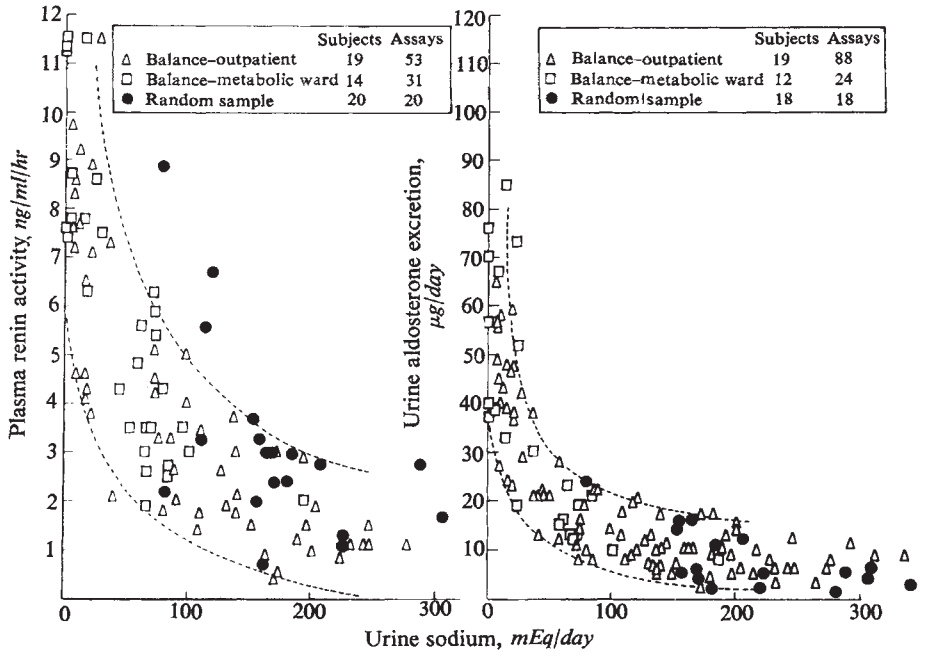

Fig. 1. *Relationship of plasma renin activity and 24-hr urinary aldosterone excretion to the concurrent daily rate of urine sodium excretion in normal subjects.* Reprinted from [50].

relationship inscribed by changes in renin and aldosterone activity in relation to urine sodium excretion strongly suggests that these two hormones play an important role in sodium conservation since their activity increases sharply during sodium depletion.

However, a question which remains unresolved is whether or not the two hormones play any role in sodium homeostasis when sodium intake is relatively high. To investigate this question, the data presented in Fig. 1 were replotted [5]. The mean urinary sodium excretion associated with a given range of renin or aldosterone activity was calculated and the mean sodium excretion for each increment of hormone activity and its SD were plotted.

As illustrated in Fig. 2, under circumstances of sodium loading, when both renin and aldosterone

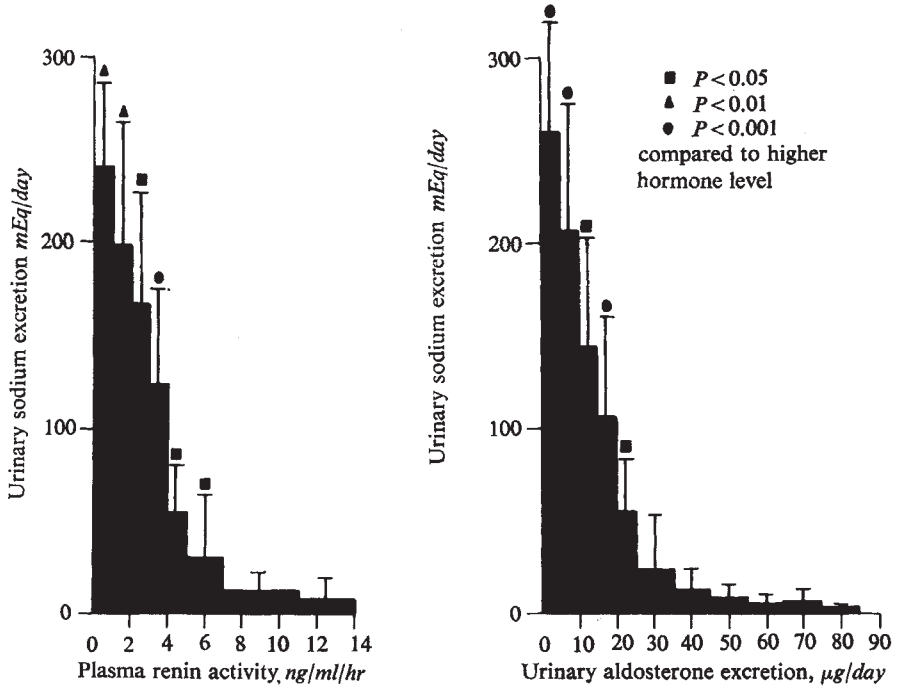

Fig. 2. *Data from Fig. 1 are replotted: mean urinary sodium excretion for given ranges of plasma renin activity and urinary aldosterone excretion.* Differences in sodium excretion are significant at all the higher rates of sodium excretion suggesting that aldosterone continues to exert a regulatory effect on urinary sodium excretion even at low levels of secretory activity. Reprinted from [5].

secretion are low, the concentrations of the two hormones continue to be closely inversely related to sodium excretion and to change in concert with fluctuations in sodium excretion. Thus, when normal subjects had a plasma renin activity from 1 to 2 ng/ml/hr, mean sodium excretion was found to be in the region of 200 mEq/day. However, at plasma renin activities of less than 1 ng/ml/hr, mean sodium excretion was quite a bit higher—in this study, approximately 250 mEq/day. Statistical treatment of the differences in these mean values indicates that they are highly significant at all of the higher rates of sodium excretion. Entirely similar results were obtained from an analysis of the relationships between sodium excretion rates and rates of aldosterone excretion during sodium loading.

These data suggest that changes in the rates of both renin and aldosterone secretion remain physiologically relevant even at very low levels of secretory activity. Thus, the renin-aldosterone axis continues to exert a regulatory effect on urine sodium excretion over the whole range of sodium intakes. This impression, that the two hormones participate in the response to sodium loading, is contrary to a widely held view that they are idling or virtually inoperative at the lower levels.

Direct effect of changes in potassium balance on aldosterone. Potassium administration has long been known to increase and potassium depletion to retard the secretion of aldosterone [6–9]. This was first demonstrated in dogs [6, 7] and it has been described in sheep [9], rats [10] and man [8]. Small increases in plasma potassium concentration of the order of 0.3 mEq/liter are often sufficient to produce sharp rises in aldosterone secretion [11].

The stimulation of aldosterone secretion by potassium appears to be quite independent of that produced by the renin-angiotensin system since it has been shown to occur in the presence of falling plasma renin activity [12]. This is illustrated in Fig. 3 in which a normal human subject exhibited a striking increase in aldosterone secretion when potassium intake was increased. At the same time, potassium suppressed plasma renin activity by direct action on the kidneys. Presumably, the adrenal cortical responses to potassium administration or deprivation are mediated by subtle changes in plasma potassium ion concentrations which may not always be apparent in randomly collected plasma samples.

Hormonal control of sodium and potassium homeostasis. The data just presented allow the construction of a scheme for hormonal control of sodium and potassium balance [8, 13]. The upper panel of Fig. 4 presents a "double-cycle feedback" system. For simplicity, angiotensin has been omitted since a large body

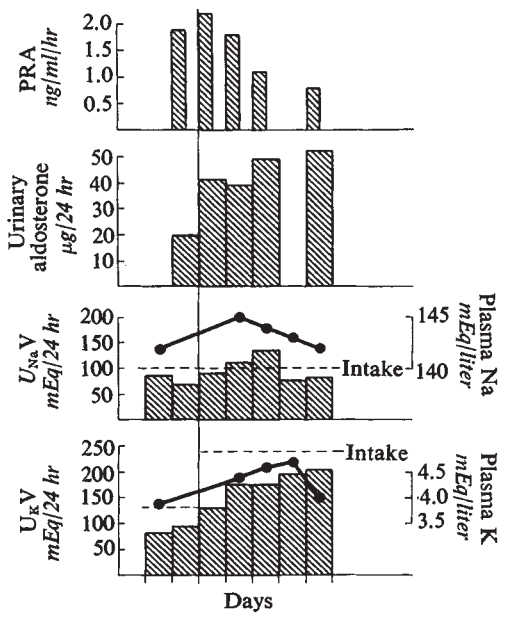

Fig. 3. *Effect of potassium loading on plasma renin activity (PRA), aldosterone and sodium balance in a normal man.* Increased potassium intake markedly stimulated aldosterone excretion while suppressing PRA. Slight natriuresis was observed during the second the third days of K^+ administration despite the marked elevation of aldosterone activity. Reprinted from [12].

of evidence indicates that the plasma concentration of this hormone is determined by changes in plasma renin activity.

1) The sodium cycle. The outer cycle of Fig. 4 (upper panel) describes the system for regulation of sodium balance via changes in renin and aldosterone secretion. In this cycle, any stimulus producing sodium or volume depletion activates renal renin secretion and this in turn stimulates aldosterone secretion. Aldosterone then causes sodium retention with attendant hydremia, and this effect, by restoring renal perfusion, operates to turn off the original signal for renin secretion and bring the aldosterone secretory rate back to the null point.

2) The potassium cycle. The inner cycle describes the hormonal system which simultaneously maintains potassium balance. Ingested potassium ions, by raising plasma potassium concentration, stimulate aldosterone secretion. Aldosterone, in turn, by acting on the renal tubules, restores plasma potassium concentration to normal by promoting renal potassium excretion. As potassium concentrations in the blood fall, aldosterone secretion is again turned off and restored to the null point, thus completing a closed-loop negative feedback system. Simultaneously, changes in plasma potassium concentration also produce direct effects on

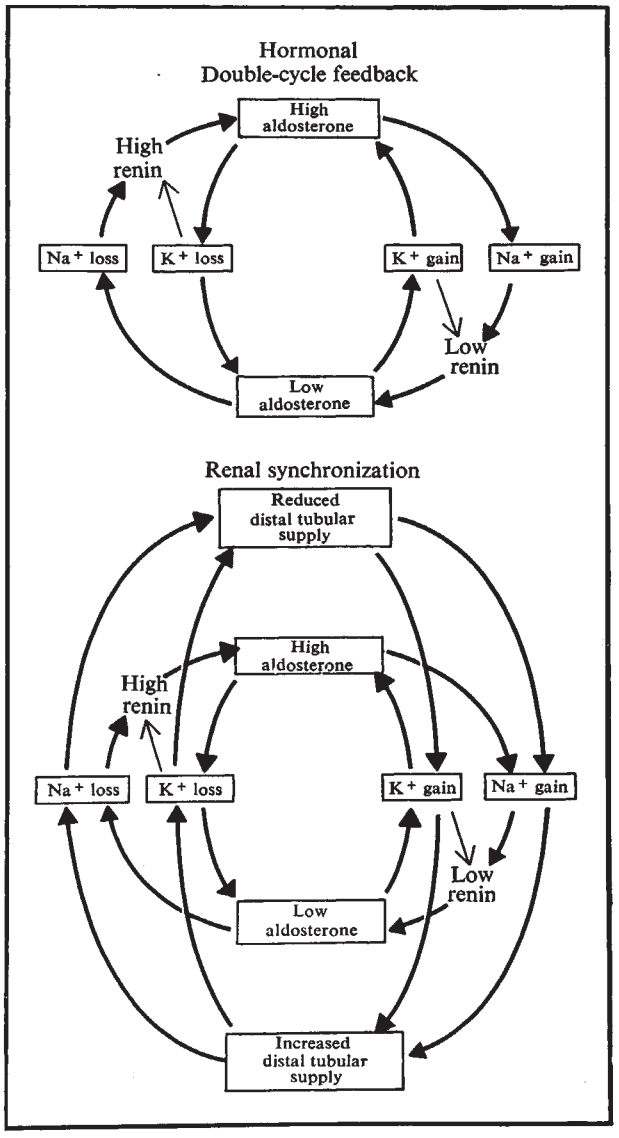

Fig. 4. Upper panel: *Interrelationship of the renin-aldosterone hormonal system with changes in sodium and potassium balance.* Lower panel: *Coordination of intrarenal physical factors with hormonal factors for sodium and potassium homeostasis.* The rate of excretion of each cation is determined by the interaction of aldosterone with distal tubular sodium supply.

renal renin secretion so that a rising plasma potassium concentration suppresses renin secretion and vice versa [12]. The changes in renin secretion induced by changes in plasma potassium concentration may perhaps operate to amplify or retard the intrarenal capacity for excretion of potassium. However, more information is needed to test this suggestion.

3) A problem with the proposed hormonal double-cycle: The response to sodium depletion. Since aldosterone acts on the kidney tubules to conserve sodium and at the same time to promote potassium elimination, one might expect that any change in aldosterone activity would lead to a change in the balance of both cations. Hence, one would predict from Fig. 4 that increases in aldosterone secretion—in response to either sodium depletion or increased dietary K^+ intake—would always cause both sodium retention and potassium loss and, conversely, decreases in aldosterone would lead to both hyperkalemia and sodium wastage, irrespective of whether the stimulus was sodium excess or potassium deprivation. Actually, these imbalances do not happen.

To understand the phenomenon, let us consider in more detail what actually happens in response to sodium deprivation. Here increased aldosterone would be expected to induce kaliuresis as it works to defend against sodium depletion. In fact, our studies [6, 13–15] and those of others [16] indicate that the converse actually occurs, i.e., there is a tendency for potassium to be retained. The influence of sodium depletion on potassium balance in a study of five normal subjects is illustrated in Fig. 5. During nine days of sustained sodium deprivation, as expected, the concentrations of both renin and aldosterone rose serially. However, despite the hyperaldosteronism, potassium balance became slowly, but progressively, positive so that a mean accumulation of some 60 mEq of K^+ occurred. This

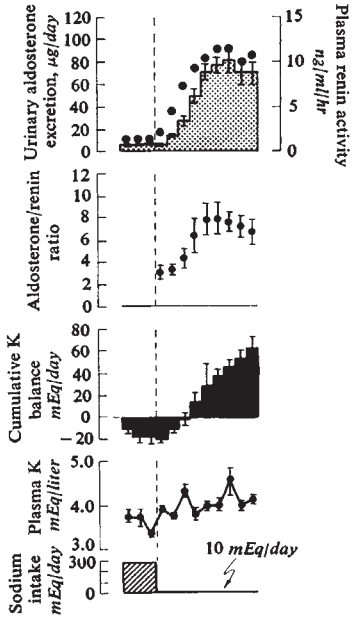

Fig. 5. *Effect of sodium depletion on aldosterone excretion and potassium balance—combined results in five normal subjects.* Despite the hyperaldosteronism induced by sodium depletion, potassium balance became progressively positive. Therefore, other factors must counterbalance the kaliuretic action of aldosterone. Reprinted from [13].

positive balance is to be contrasted with the neutral or slightly negative K^+ balance during the three-day control period. Thus, sodium depletion and associated induced hyperaldosteronism did not induce the predicted hypokalemia but actually caused potassium retention with a tendency towards hyperkalemia.

The converse relationship [13, 14, 17, 18] is illustrated by the study presented in Fig. 3, in which increased potassium administration to a normal subject induced a slight transient natriuresis rather than the sodium retention which might be predicted in response to potassium-induced hyperaldosteronism.

It is apparent then that the two concurrent renal actions of aldosterone do not result in conservation of one electrolyte at the expense of the other. Therefore, sodium and potassium homeostasis cannot be explained solely in terms of aldosterone action. However, the nature of the control system can perhaps be understood if the concurrent and complementary effects of changes in intrarenal physical factors are taken into account [13].

Intrarenal factors which affect sodium and potassium excretion and how they react to changes in ion availability

To understand the coordinated interaction of the intrarenal physical and biochemical changes with hormonal changes, it is first necessary to describe these intrarenal changes and their effects per se on sodium and potassium excretion. Second, one must in turn consider how changes in availability of sodium or potassium, or both, affect these intrarenal mechanisms.

Intrarenal factors affecting sodium and potassium excretion. 1) Sodium excretion. The amount of sodium excreted in the urine is a function of the glomerular filtration rate (GFR) of sodium minus the net sum of sodium reabsorbed from the proximal tubule, loop of Henle, distal convoluted tubule and collecting duct. Theoretically, increases in the filtration rate of sodium would increase, and decreases would reduce, the amount of sodium excreted into the urine. However, because increases or decreases in filtration rate are always accompanied by commensurate changes in proximal sodium reabsorption (glomerular tubular balance), changes in GFR do not result in commensurate increases in sodium excretion and, instead, the effect is dampened. Despite this, fluctuations in GFR can result in incremental changes in the amount of sodium delivered out of the proximal tubule.

It is possible that changes in GFR are mediated in part by changes in circulating angiotensin II. Deviations in either sodium or potassium balance affect renal renin secretion and, thus, angiotensin II formation, so that an increase in intake of either cation depresses, and depletion of either cation increases, renal renin secretion [2, 12, 14]. Angiotensin II infusions have long been known to reduce GFR and renal blood flow [19–21]. Filtration fraction often rises, suggesting a slight efferent arteriolar predominance. Conversely, infusion into sodium-depleted dogs of a specific angiotensin II inhibitor [22] resulted in increased renal blood flow, raising again the possibility of a renal hemodynamic regulatory effect of the vasoactive peptide. Other investigators have proposed that angiotensin is involved in intrarenal regulation of GFR mediated by a sodium-sensitive macula densa signal to the adjacent afferent arteriole [23]. However, these proposals remain a subject of controversy [24] and they do not seem useful or necessary for explaining the phenomena discussed herein.

The rate of sodium reabsorption in the proximal tubule, as well as being proportional to GFR, is also affected by changes in other intrarenal physical factors. The increased intrarenal hydrostatic pressure which occurs during expansion of extracellular fluid volume can markedly reduce sodium reabsorption in the proximal tubule [25, 26] by affecting the rate at which the reabsorbed sodium is removed by the peritubular capillaries [27]. Increased hydrostatic pressures can result in increased back-flux of sodium into the proximal tubule [28]. In addition, hemodilution, which also occurs with increased sodium balance and volume expansion, results in reduction in oncotic pressure in the peritubular capillaries [29]. This effect has also been shown to cause increased back-flux of sodium and, thus, reduces net proximal tubular sodium reabsorption. Altogether then, by these mechanisms, volume expansion decreases proximal tubular sodium reabsorption and dehydration and sodium depletion increases it [30].

Increases or decreases in potassium balance also operate to increase or decrease proximal tubular sodium reabsorption, respectively [31, 32]. The mechanism whereby this effect occurs might be related to an accompanying swelling or dehydration of cells, in association with an excess or deficiency of potassium. It has been hypothesized that proximal tubular sodium transport occurs, at least in part, between cells, i.e., across the tight junction [28]. It is not unreasonable to speculate that when cells are swollen, less sodium can be transported across the tight junction because of mechanical hindrance. Conversely, dehydration would result in opening of tight junctions and greater facility for sodium reabsorption.

Most evidence suggests that sodium transport in the loop of Henle and ascending limb is load-dependent

and does not fluctuate in response to changes in either sodium or potassium balance [33]. Altogether then, changes in the intake of either sodium or potassium induce changes in intrarenal function, i.e., in GFR and proximal sodium reabsorption, which can result in increases or decreases in the amount of sodium delivered out of the proximal tubule. These changes affect distal sodium delivery and, *ceteris paribus*, could produce commensurate changes in urine sodium excretion.

2) Potassium excretion. Most available evidence suggests that filtered potassium is almost completely reabsorbed before reaching to the distal convoluted tubule [33]. Urine potassium excretion appears to result mainly from distal tubular secretion, counterbalanced by some distal tubular reabsorption [28].

Intrarenal physical factors affect potassium excretion because, as already discussed herein, they work to determine the amount of sodium presented to the distal convoluted tubule where potassium is secreted. Evidence suggests that changes in distal sodium supply can markedly affect potassium excretion [33, 34]. Since sodium reabsorption in the distal tubule is not accompanied by commensurate chloride reabsorption, a negative electrochemical gradient develops and potassium passes from the cells into the tubular urine in an attempt to restore electroneutrality [35, 36]. Hence, the increase in net sodium reabsorption which occurs in response to an increase in distal sodium supply would result in greater electronegativity and, thus, an augmentation of net potassium secretion. Therefore, increases in distal tubular sodium supply, by increasing net distal sodium reabsorption, augment potassium elimination, and decreases in sodium supply reduce potassium excretion.

Another intrarenal change which could affect potassium excretion is the availability of intracellular potassium [28]. The amount of potassium secreted in response to a given electrochemical gradient could vary according to available intracellular potassium so that, under circumstances in which intracellular potassium concentration is increased, potassium excretion would be augmented, and vice versa. Since intracellular potassium (in general and in renal tubular cells in particular) is likely to increase and decrease with plasma concentrations, this mechanism per se probably operates systemically and intrarenally to aid in potassium homeostasis.

Effects of changes in sodium and potassium-balance on the intrarenal physical factors. 1) Distal sodium supply. As indicated already, changes in this quantity are larely consequent to changes in either GFR or in proximal tubular sodium reabsorption.

a) Glomerular filtration rate. Sodium depletion and sodium loading decrease or increase filtration rate, respectively [37–39]. In recent years the importance of changes in GFR has been somewhat overshadowed by increased emphasis on the importance of changes in fractional sodium reabsorption in the proximal tubule. However, a recent report by Daugharty et al [39] has reemphasized the important role of GFR in modulating the amount of sodium delivered out of the proximal tubule. During *chronic* sodium loading, changes in GFR were shown to be quantitatively more important in determining distal sodium supply than were changes in fractional proximal sodium reabsorption. However, the response to *acute* changes in sodium balance was relatively more dependent on changes in fractional proximal tubular sodium reabsorption.

The effects of changes in potassium balance on GFR are less well defined, but there is evidence that potassium depletion significantly reduces GFR [40, 41]. The lack of evidence that increased potassium balance potentiates the GFR may be accounted for by the toxic effect on the heart of the doses of potassium used in experimental studies. This could result in a fall in cardiac output, decreased renal blood flow and reduction in GFR which might mask a more relevant, direct effect of mild potassium excess to stimulate GFR. A recent study reaffirms the vasodilator action of modest hyperkalemia [42].

b) Proximal tubular sodium reabsorption. In the last few years, many animal studies have demonstrated that positive sodium balance depresses fractional reabsorption of sodium in the proximal tubule [25, 26] and, conversely, that sodium depletion enhances proximal reabsorption [29].

Changes in potassium balance also have been shown to affect proximal tubular sodium reabsorption [31, 32]. Potassium depletion increases [32], and potassium loading decreases [31], proximal fractional sodium reabsorption.

Altogether then, increases in either sodium or potassium balance act to *1)* increase GFR, perhaps in part via depression of angiotensin II concentration; and *2)* to depress proximal tubular sodium reabsorption. These changes work together to increase sodium supply to the distal tubule. Conversely, decreases in either sodium or potassium intake reduce the amount of sodium delivered to the distal tubule (Fig. 4, lower panel).

2) Effect of changes in sodium or potassium balance on intracellular potassium. There is evidence to suggest that during chronic potassium loading adaptation occurs so that the body can remove potassium from the blood more rapidly and also can excrete larger amounts more efficiently [17, 43–45]. This may be due in part to an increase in the amount of intracellular

potassium. Increased intrarenal intracellular potassium could result in potentiation of the amount of potassium excretion which occurs in response to a given level of distal sodium reabsorption.

Giebisch, Boulpaep and Whittenbury have suggested that only a portion of intracellular potassium is available for potassium transport [28] and that during potassium loading the size of the potassium transport pool increases. They suggest that the size of the pool also may be dependent on available sodium since the amount of intracellular potassium may be a reflection of the operating effectiveness of the Na^+/K^+ exchange pump. During sodium depletion, available intracellular potassium might have a tendency to fall because of a reduction in the amount of sodium available to exchange for potassium. However, this effect may be counterbalanced or even overcompensated by positive K^+ balance and the hyperkalemia which accompanies sodium depletion [15]. The latter is in keeping with the observations that renal potassium secretory capacity is often well-maintained, albeit at higher concentrations of plasma K^+, under extreme conditions of sodium depletion [15].

According to the foregoing reasoning, intracellular potassium content would be directly affected by changes in either sodium or potassium balance. However, it is likely that relatively smaller changes in available intracellular potassium occur in response to changes in sodium balance.

Linking together hormonal and intrarenal physical factors to explain electrolyte homeostasis

Regulation of sodium balance (Fig. 4, lower panel). Regulation of sodium balance is considered herein to be accomplished by changes in distal sodium supply, an effect of changes in intrarenal physical factors, interacting with the rate of distal sodium reabsorption, an effect of changes in aldosterone [46]. Increased sodium excretion occurring in response to a positive sodium balance is accomplished by increased distal sodium supply together with reduced fractional distal sodium reabsorptive rate (i.e., via reduced aldosterone), both of which work to increase urinary sodium excretion. Conversely, sodium conservation in response to sodium deprivation is accomplished by reduced distal sodium supply coordinated with a marked increase in fractional distal sodium reabsorptive rate (i.e., increased aldosterone). Together, these two changes result in reduction in urine sodium excretion.

Regulation of potassium balance (Fig. 4, lower panel). The regulation of potassium balance is the integrated result of *1*) changes in distal sodium supply, *2*) changes in fractional distal sodium reabsorption (aldosterone determined) and *3*) changes in intracellular potassium. The first two factors in determining net distal sodium reabsorption become a prerequisite for potassium secretion which is then further determined by the third factor (not illustrated in Fig. 4).

As already indicated, positive potassium balance causes increased distal sodium supply. Increases in distal sodium supply per se favor increased net distal sodium reabsorption. A larger electrochemical gradient thereby develops which allows more potassium to be secreted. A concurrent potassium-induced elevation in aldosterone secretion increases the fraction of distal sodium supply reabsorbed, and this also potentiates potassium secretion. Moreover, the potassium secretion rate is further potentiated by the increased renal intracellular potassium available for secretion.

Conversely, with potassium deprivation, conservation is accomplished (*vide supra*) by *1*) diminishing distal tubular sodium supply and *2*) diminished net distal reabsorptive rate from the reduced supply and lowered aldosterone. A fall in distal sodium reabsorption together with *3*) a reduction in available intracellular potassium can result in a marked fall in net potassium secretion.

Effect of defending sodium balance on potassium excretion. 1) Sodium loading. Sodium loading induces increased distal sodium supply and reduced aldosterone activity (Fig. 6, upper panel). By itself, increased distal sodium supply would result in increased net distal sodium reabsorption. However, the concurrent reduction in aldosterone activity lowers the fraction of the increased distal sodium load which is reabsorbed and thus allows more sodium to be excreted. At the same time, the hormonal and physical changes counterbalance each other so that no change in *net* distal sodium reabsorption occurs. As long as net distal sodium reabsorptive rate is unchanged, potassium excretion should remain constant. Therefore, potassium excretion need not change in the face of wide fluctuations in sodium balance since counterbalancing physical and hormonal changes keep net distal sodium reabsorption constant.

2) Sodium depletion. In the same fashion, net distal sodium reabsorption is unchanged during sodium deprivation since the induced fall in distal sodium supply is almost exactly counterbalanced by a marked increase in fractional sodium reabsorption due to the increased aldosterone activity. Accordingly, here too, since net distal sodium reabsorption is unchanged, potassium homeostasis is not disturbed by the defense of sodium balance.

Effect of defending potassium balance on sodium excretion. 1) Potassium loading (Fig. 6, lower panel).

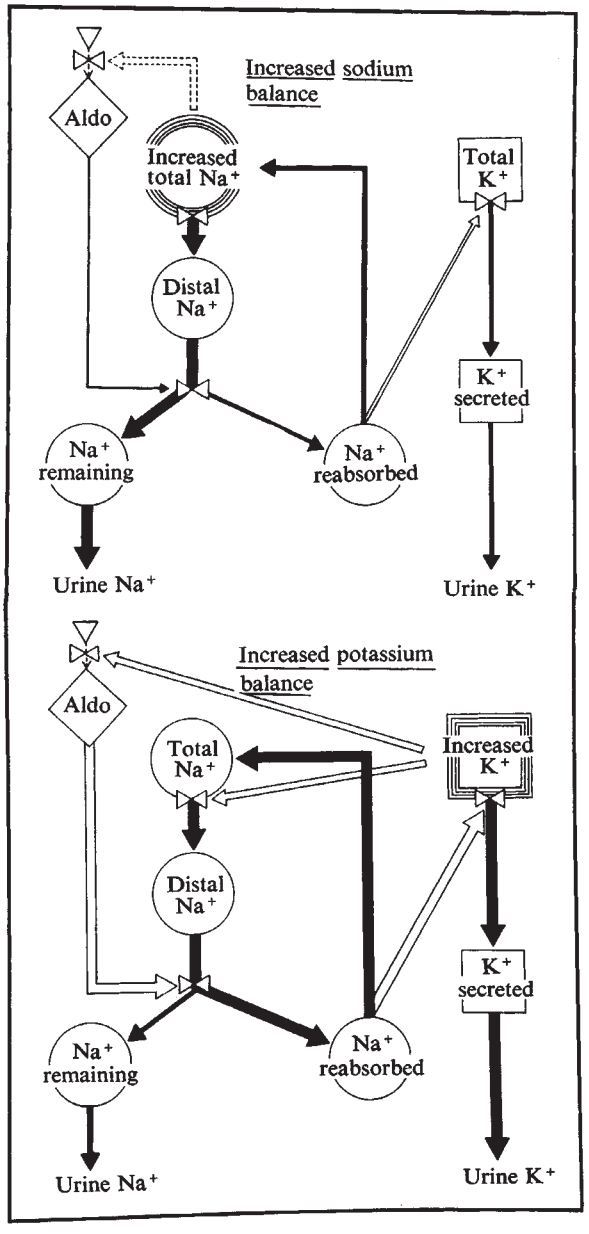

Fig. 6. *Interrelationship of distal sodium supply with aldosterone activity during increases in sodium and potassium balance.* ▷◁=rate constant; *dotted arrow*=suppressive effect; *open arrow*=effect of the induced change on the rate constant; *closed arrows*=flow of sodium and potassium ions. Width of arrows represents magnitude of effect. Both increased sodium (*upper panel*) and potassium (*lower panel*) cause increased distal sodium supply. The concurrent fall in aldosterone associated with positive sodium balance allows most of the increased distal sodium load to pass into the urine. However, the increased aldosterone associated with positive potassium balance causes most of the distal sodium to be reabsorbed. This prevents sodium loss while promoting increased negative electrochemical gradient and, thus, increased potassium excretion.

Potassium loading has been shown to cause increased distal sodium supply together with an increased aldosterone secretion rate. Both of these changes work to augment the distal tubular sodium reabsorptive rate which enables increased potassium excretion to handle the increased load. At the same time, sodium balance is maintained because the increased distal sodium reabsorption almost exactly compensates for the increased load of sodium presented to the distal tubule, resulting in little net change in urine sodium excretion. Thus, major shifts in the location of intrarenal sodium transport for the purpose of accommodating potassium homeostasis need not be reflected by any change at all in sodium excretion in the final urine.

2) Potassium depletion. Sodium balance is also maintained during potassium deprivation. Here an induced increase in proximal sodium reabsorption with reduction in distal sodium supply is almost exactly offset by a reduction in distal sodium reabsorptive rate (from lowered aldosterone). The latter allows the conservation of potassium to occur while at the same time maintaining sodium excretion constant.

The simultaneous defense of sodium and potassium balance. When both sodium and potassium intake increase together, little or no change occurs in aldosterone secretion since the stimulatory effect of potassium is offset by the dampening action of positive sodium balance. However, marked increases in distal sodium supply would be expected to occur in response to this double stimulus to depress proximal sodium reabsorption. This results in augmentation of net distal sodium reabsorptive rate, which facilitates potassium excretion while urine sodium excretion is increased because the increased sodium load is not offset by any change in aldosterone activity. Thus, both sodium and potassium excretions are markedly elevated simply by induced changes in intrarenal physical factors.

A similar response occurs when both cations are in short supply. Aldosterone activity again remains unchanged while sodium and potassium excretion are reduced to a minimum by the double stimulus for increased proximal sodium reabsorption with consequent marked reductions in distal sodium supply.

When the intake of the two electrolytes is changed to the same degree in opposite directions, balance is maintained by holding the distal sodium supply constant in the face of marked changes in aldosterone secretion. For example, when sodium depletion is combined with potassium administration, aldosterone secretion becomes greatly enhanced from the double stimulus, so that reabsorption of an unaltered distal sodium supply is almost complete, thus allowing for maximum potassium excretion while reducing sodium excretion to a minimum.

Mathematical expression of the interaction of aldosterone with distal sodium supply

To examine this analysis in mathematical terms, the amount of distal sodium left unreabsorbed (i.e., urine sodium excretion) can be considered to be determined by the *quotient: distal sodium supply/aldosterone activity*, whereas renal potassium excretion (a function of the amount of distal sodium reabsorbed) can be considered to be determined by the *product: distal sodium supply* × *aldosterone activity*.

It can be readily appreciated that by varying two numbers, an infinite number of combinations exists which can combine to give a common product. However, depending on the values chosen, the quotient of the two numbers would be widely different. Applying this simple mathematical concept to maintenance of sodium and potassium balance, an infinite number of combinations of distal sodium supply and aldosterone activity theoretically exist which can result in a constant product while allowing wide variation in the amount of sodium being excreted (variable quotient). Also, theoretically an infinite number of combinations of distal sodium supply and aldosterone activity exist which can result in a constant amount of sodium being excreted (constant quotient) while allowing wide variation in the amount of potassium being excreted (variable product). In addition, simultaneous variations in both the product and the quotient can accomplish concurrent changes in both sodium and potassium excretion. Examples of these relationships are depicted using model numbers in Table 1.

Table 1. Model numbers illustrating the relationship of aldosterone and distal sodium supply to urinary sodium and potassium excretions

Dietary intake		*Distal sodium supply*	*Aldosterone*	$U_{Na}V$[a]	U_KV[b]
Sodium	*Potassium*				
Varied sodium intake, constant potassium intake					
High	Normal	31.6	0.316	100	10
Normal	Normal	10.0	1.0	10	10
Low	Normal	3.16	3.16	1	10
Varied potassium intake, constant sodium intake					
Normal	High	31.6	3.16	10	100
Normal	Normal	10.0	1.0	10	10
Normal	Low	3.16	0.316	10	1
Varied intake of both sodium and potassium					
High	High	100	1	100	100
Low	Low	1	1	1	1
High	Low	10	0.1	100	1
Low	High	10	10	1	100

[a] Urinary excretion of sodium ($U_{Na}V$) is calculated from distal sodium supply/aldosterone.
[b] Urinary excretion of potassium (U_KV) is calculated from (distal sodium supply × aldosterone).

The preceding analysis has outlined how two different mechanisms, both of which affect the balance of sodium and potassium ions, coordinate and interact with each other to maintain appropriate overall balance of each ion by allowing appropriate variations in the excretion of each ion. Mathematical soundness of the postulated interactions appears to lend weight to the hypothesis but does not necessarily prove its validity. Obviously, more direct experimental support is needed [46]. In addition, the hypothesis does not take into account recent evidence that other mechanisms are operative in the collecting duct which modify urine sodium excretion [47, 48]. These other mechanisms include a possible natriuretic hormone shown to operate in the distal tubule [49]. However, these other factors may act to further modify urine sodium excretion without invalidating the present overall concept of an interaction between humoral and physical factors, which contributes to maintenance of sodium and potassium balance.

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